Empirical tuberculosis therapy versus isoniazid in adult outpatients with advanced HIV initiating antiretroviral therapy (REMEMBER): a multicountry open-label randomised controlled trial

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Summary

Background Mortality within the first 6 months after initiating antiretroviral therapy is common in resource-limited settings and is often due to tuberculosis in patients with advanced HIV disease. Isoniazid preventive therapy is recommended in HIV-positive adults, but subclinical tuberculosis can be difficult to diagnose. We aimed to assess whether empirical tuberculosis treatment would reduce early mortality compared with isoniazid preventive therapy in high-burden settings.

Methods We did a multicountry open-label randomised clinical trial comparing empirical tuberculosis therapy with isoniazid preventive therapy in HIV-positive outpatients initiating antiretroviral therapy with CD4 cell counts of less than 50 cells per μL. Participants were recruited from 18 outpatient research clinics in ten countries (Malawi, South Africa, Haiti, Kenya, Zambia, India, Brazil, Zimbabwe, Peru, and Uganda). Individuals were screened for tuberculosis using a symptom screen, locally available diagnostics, and the GeneXpert MTB/RIF assay when available before inclusion. Study candidates with confirmed or suspected tuberculosis were excluded. Inclusion criteria were liver function tests 2·5 times the upper limit of normal or less, a creatinine clearance of at least 30 mL/min, and a Karnofsky score of at least 30. Participants were randomly assigned (1:1) to either the empirical group (antiretroviral therapy and empirical tuberculosis therapy) or the isoniazid preventive therapy group (antiretroviral therapy and isoniazid preventive therapy). The primary endpoint was survival (death or unknown status) at 24 weeks after randomisation assessed in the intention-to-treat population. Kaplan-Meier estimates of the primary endpoint across groups were compared by the z-test. All participants were included in the safety analysis of antiretroviral therapy and tuberculosis treatment. This trial is registered with ClinicalTrials.gov, number NCT01380080.

Findings Between Oct 31, 2011, and June 9, 2014, we enrolled 850 participants. Of these, we randomly assigned 424 to receive empirical tuberculosis therapy and 426 to the isoniazid preventive therapy group. The median CD4 cell count at baseline was 18 cells per μL (IQR 9–32). At week 24, 22 (5%) participants from each group died or were of unknown status (95% CI 3·5–7·8) for empirical group and for isoniazid preventive therapy (95% CI 3·4–7·8); absolute risk difference of –0·06% (95% CI –3·05 to 2·94). Grade 3 or 4 signs or symptoms occurred in 50 (12%) participants in the empirical group and 46 (11%) participants in the isoniazid preventive therapy group. Grade 3 or 4 laboratory abnormalities occurred in 99 (23%) participants in the empirical group and 97 (23%) participants in the isoniazid preventive therapy group.

Interpretation Empirical tuberculosis therapy did not reduce mortality at 24 weeks compared with isoniazid preventive therapy in outpatient adults with advanced HIV disease initiating antiretroviral therapy. The low mortality rate of the trial supports implementation of systematic tuberculosis screening and isoniazid preventive therapy in outpatients with advanced HIV disease.

Funding National Institutes of Allergy and Infectious Diseases through the AIDS Clinical Trials Group.

Introduction

Introduction and expansion of antiretroviral therapy programmes have saved millions of lives among HIV-positive individuals in resource-limited settings.[1] Despite these successes, individuals with advanced HIV disease continue to present for care, and up to 17% of adults die in the first year after antiretroviral therapy initiation.[2] Risk factors for early mortality after antiretroviral therapy initiation include a low CD4 cell count, low body-mass index, and anaemia, with those having a CD4 cell count of less than 50 cells per μL having the highest risk of any individual factor.[2]

Tuberculosis is the most common cause of mortality in HIV-positive individuals and both prevalent and incident

Research in context

Evidence before this study

We searched PubMed for articles published up to Feb 9, 2016, in any language, that used a randomised trial design to test the hypothesis that empirically treating HIV-positive individuals with tuberculosis who did not have clinical or microbiological evidence of tuberculosis disease would reduce early mortality after antiretroviral therapy initiation using the search terms: "HIV-1", "tuberculosis", "mortality", "antiretroviral therapy", "empiric therapy", and "randomized trial". No published randomised trials of empirical tuberculosis therapy were identified.

WHO guidelines advocate use of symptom screening and isoniazid preventive therapy for 6 to 36 months in HIV-positive individuals in whom tuberculosis is not found after screening. However, isoniazid preventive therapy is poorly implemented in most settings due partly to data showing that patients with HIV or tuberculosis might have few symptoms, which could result in treating patients with subclinical tuberculosis with a single drug. Additionally, although the WHO recommends the Cepheid GeneXpert MTB/RIF (Xpert MTB/RIF) assay as a diagnostic tool to improve identification of tuberculosis, and tuberculosis drug resistance in HIV-associated tuberculosis, availability remains sparse and implementation of the test has not been associated with reduced mortality in randomised trials to date. Empirical tuberculosis treatment, based on clinical symptoms without microbiological confirmation in those at high risk of tuberculosis and death, is an alternative approach to managing these patients and has been recommended for study by the WHO. At the time of study inception, however, no randomised studies had assessed this strategy for reducing early antiretroviral therapy mortality in HIV-infected outpatients presenting for antiretroviral therapy initiation.

Three clinical trials assessing empirical tuberculosis therapy are ongoing. These include the systematic empirical versus test-guided antituberculosis treatment impact in severely immunosuppressed HIV-infected adults initiating antiretroviral therapy with CD4 cell counts of less than 100 cells per μL; the tuberculosis fast track study; and the REMEMBER study, of which the 24-week results are presented here. Although the design of each of these studies is different, all include HIV-positive populations at high risk of early mortality and use of empirical tuberculosis treatment. The REMEMBER study addresses the question of whether outpatients with advanced HIV disease who are not diagnosed with tuberculosis after screening with existing methods should be empirically treated for tuberculosis or started on isoniazid preventive therapy as recommended by WHO.

Added value of this study

REMEMBER is the first completed clinical trial that addresses whether outpatients with advanced HIV disease living in settings with a high burden of tuberculosis who screen negative for tuberculosis should initiate isoniazid preventive therapy or be treated empirically for tuberculosis, and it is the only empirical tuberculosis clinical trial that includes an isoniazid group. This study was done at 18 diverse sites in ten countries that probably reflect conditions encountered by clinicians attempting to diagnose and treat tuberculosis in patients with advanced HIV disease in resource-limited settings. We found no beneficial effect of empirical treatment on mortality. Overall, the mortality rate in the study was lower than what antiretroviral therapy programmes have reported in observational studies, probably reflecting the clinical trial care setting. There was a suggestion of possible harm in the empirical group with respect to incident tuberculosis and HIV disease progression. Isoniazid preventive therapy was safe and well tolerated.

Implications of all the available evidence

In settings where routine symptom screening is done in outpatients presenting to initiate antiretroviral therapy, diagnostics are accessible, and close follow-up is possible, there is no benefit to empirical tuberculosis treatment compared with the WHO recommendation of the use of isoniazid preventive therapy. Additionally, this trial shows that isoniazid preventive therapy can be safely given to HIV-positive individuals with advanced disease. The results strongly suggest that antiretroviral therapy programmes should enhance routine tuberculosis symptom screening and implementation of isoniazid preventive therapy, even for individuals with low CD4 cell counts.

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tuberculosis infections are major contributors to early mortality in patients presenting to outpatient settings to initiate antiretroviral therapy.[3] Up to 70% of patients with tuberculosis in sub-Saharan Africa are HIV positive, and tuberculosis incidence rates after antiretroviral therapy initiation are high, particularly in those with advanced HIV disease.[4,5] Autopsy studies[6] from sub-Saharan Africa, southeast Asia, and the Americas identified tuberculosis as the primary or contributing cause of mortality in most cases with nearly half of the tuberculosis cases undiagnosed pre-mortem. Strategies addressing tuberculosis in patients at high risk of early mortality worldwide are urgently needed.

Patients with HIV often do not have classic symptoms and signs of tuberculosis, which complicates diagnosis. WHO-endorsed symptom screening for tuberculosis, based on cough, fever, weight loss, and night sweats, misses two in ten tuberculosis cases in HIV-positive individuals.[7] In resource-limited settings where tuberculosis is common, patients with positive symptom screens are usually assessed with sputum staining for acid-fast bacilli, which has low sensitivity in HIV-positive individuals with low CD4 counts.[8] Likewise, patients with advanced HIV might have small changes in chest radiography. The GeneXpert MTB/RIF assay (Xpert MTB/RIF, Cepheid [Sunnyvale, CA, USA]), has improved

the sensitivity of sputum testing,[9] but availability of this test remains scarce,[10] and implementation of Xpert MTB/RIF alone has not decreased HIV-associated and tuberculosis-associated mortality.[11–13] Limitations of existing diagnostics contribute to major ongoing challenges in diagnosing and treating HIV-associated tuberculosis in resource-limited settings.

Expanded use of empirical tuberculosis treatment, defined as treatment in absence of microbiological confirmation of tuberculosis disease, has emerged as one potential approach to reduce tuberculosis-associated mortality. WHO recommends that patients who screen negative for tuberculosis be placed on isoniazid preventive therapy, and empirical tuberculosis therapy only be used for seriously ill patients in peripheral settings in whom initial tests are negative.[14] However, the optimum approach for managing patients at high risk of HIV-associated tuberculosis and early mortality after antiretroviral therapy initiation is uncertain. Studies[15] have provided further evidence indicating that isoniazid preventive therapy alone might substantially reduce the risk of tuberculosis-associated mortality in HIV,[15] but concerns about the tolerability of isoniazid preventive therapy and promotion of drug resistance in patients with sub-clinical tuberculosis have reduced the uptake of this intervention. For patients with advanced immunosuppression, an alternative strategy relevant to high-burden settings would be to empirically treat tuberculosis in all severely immunosuppressed patients who are not found to have tuberculosis after screening, even if not seriously ill. This approach could decrease early mortality by addressing undiagnosed, untreated tuberculosis and, with the use of rifampin, increase durability of tuberculosis preventive therapy and treat or prevent severe bacterial infections. We designed the REMEMBER (reducing early mortality and early morbidity by empirical tuberculosis treatment regimens) study to assess whether empirical tuberculosis treatment will reduce early mortality compared with isoniazid preventive therapy in participants with advanced HIV disease presenting for antiretroviral therapy initiation in settings where tuberculosis is common.

For **protocol** see https://clinicaltrials.gov/ct2/show/NCT01380080?term=NCT01380080&rank=1

Methods

Study design and participants

In this open-label randomised controlled trial, we enrolled 851 HIV-positive antiretroviral therapy-naive individuals from 18 outpatient research clinics in ten countries (Malawi, South Africa, Haiti, Kenya, Zambia, India, Brazil, Zimbabwe, Peru, and Uganda), with 77% of the enrolment occurring in sub-Saharan Africa, aged 13 years or older with CD4 cell counts of less than 50 cells per μL who did not have evidence of active tuberculosis, and were eligible for either isoniazid preventive therapy or empirical tuberculosis treatment. All 18 sites reported a tuberculosis incidence of more than 100 per 100 000 person-years and had antiretroviral therapy programmes with documented high early mortality rates (>10–20 per 100 person-years) in outpatient populations.

Inclusion criteria included having liver function tests 2·5 times the upper limit of normal or less, a creatinine clearance of at least 30 mL/min, and a Karnofsky score of at least 30, to facilitate inclusion of participants with advanced HIV presenting to antiretroviral therapy clinics who were able to rapidly initiate both antiretroviral therapy and tuberculosis treatment or isoniazid preventive therapy. To decrease the possible influence of HIV or tuberculosis drug resistance on outcomes, exclusion criteria included use of single dose nevirapine in the preceding 2 years, receipt of tuberculosis treatment within 96 weeks before study entry, or isoniazid preventive therapy within 48 weeks before study entry, and a history of household exposure to multidrug-resistant tuberculosis. Full eligibility criteria are included in the protocol. Sites obtained ethical approval from local ethics committees. All participants provided written informed consent.

Randomisation and masking

Participants were randomly assigned (1:1) to either the empirical group (antiretroviral therapy and empirical tuberculosis therapy) or the isoniazid preventive therapy group (antiretroviral therapy and isoniazid preventive therapy). The randomisation sequence was generated by a computer at the AIDS Clinical Trial Group Data Management Center. Randomisation was balanced by clinical trial unit and stratified according to CD4 cell count (<25 cells per μL *vs* ≥25 cells per μL) and presence of any of the following prognostic factors: reportable hospital admission within the past 30 days, a body-mass index of less than 18·5 kg/m², or anaemia (haemoglobin concentration <8 g/dL). Participants, site personnel, and study statisticians were not masked to group assignment. The open-label pragmatic design was chosen to reflect actual field settings where antiretroviral therapy would be combined with either empirical four-drug therapy or isoniazid preventive therapy.

Procedures

Study sites generally complied with guidelines for antiretroviral therapy initiation in their country programmes. All 18 sites initiated antiretroviral therapy for WHO stage 3 or 4 disease for patients with CD4 cell counts lower than 350 cells per μL. For standard of care tuberculosis screening, all 18 sites reported using sputum acid-fast bacilli testing screening and chest radiography, and five sites reported using the Xpert MTB/RIF assay.

Potential participants were referred to study clinics from local antiretroviral therapy clinics, many of which were co-located and some of which were fully integrated within the antiretroviral therapy programme. At the study clinics, potential participants were screened for tuberculosis before study entry with a symptom screen that included the following: cough for 2 weeks or longer, any current fever with a body temperature of more than

38°C, haemoptysis, night sweats within the past 2 weeks, unintentional weight loss of more than 10% in the past 30 days, and enlarged axillary or cervical lymph nodes. Any positive screen required further work-up per local standard of care. All sites had capacity to do acid-fast bacilli smears, chest radiography, ultrasound, mycobacterial culture, and GeneXpert; however, the use of specific tests was left up to the sites' clinicians. People who were strongly suspected to have tuberculosis or for whom screening procedures identified confirmed or probable tuberculosis were excluded. The study did not obtain information on the outcomes of people excluded from study entry. In response to a June, 2013, data safety monitoring board review, the protocol was modified to require the addition of sputum Xpert MTB/RIF assay testing for all potential participants during screening. Participants with negative symptom screens or positive screens but no microbiological or presumptive diagnosis of tuberculosis were eligible for enrolment in the study.

All participants received efavirenz-containing antiretroviral therapy with either study-provided tenofovir/emtricitabine (donated by Gilead) or locally available nucleoside reverse transcriptase inhibitors. Participants in the empirical group received self-administered, weight-adjusted, fixed-dose combination rifampin/isoniazid/ethambutol/pyrazinamide for 8 weeks, followed by fixed-dose combination rifampin/isoniazid for 16 weeks, beginning within 7 days after antiretroviral therapy initiation. Participants in the isoniazid preventive therapy group received 300 mg of isoniazid daily for 24 weeks, beginning within 7 days of antiretroviral therapy. All participants received pyridoxine.

Participants were followed up for 96 weeks. Here, we report results up to week 24. Participants attended study visits at screening, enrolment, and weeks 1, 2, 4, 8, 12, 16, 20, and 24. Signs and symptoms, antiretroviral therapy modifications, concomitant medications, and clinical events as defined by AIDS Clinical Trials Group appendix 60 were obtained at each visit. Blood samples were collected to measure CD4 cell count and HIV-1 RNA levels at study entry, weeks 4, and 24, and blood for safety tests (liver function, haematology, and renal function) was collected at all visits except week 1. A sputum sample for each participant was collected and stored at study entry. After the data safety monitoring board review requiring real time Xpert MTB/RIF testing, the available stored samples collected before this requirement were retrospectively tested with the Xpert MTB/RIF assay. Participants in both groups who developed signs or symptoms of tuberculosis had tuberculosis investigations done as per locally available diagnostics, which included sputum culture tests and, for those with positive cultures, drug susceptibility testing. Those with drug-sensitive tuberculosis received weight-adjusted, fixed-dose combination rifampin/isoniazid/ethambutol/pyrazinamide for 8 weeks, followed by fixed-dose combination rifampin/isoniazid for 16 weeks. Any participant with drug-resistant tuberculosis was treated according to local standard of care. In the event of missed visits, participants were traced by telephone calls and home visits if they or their contacts could not be reached by

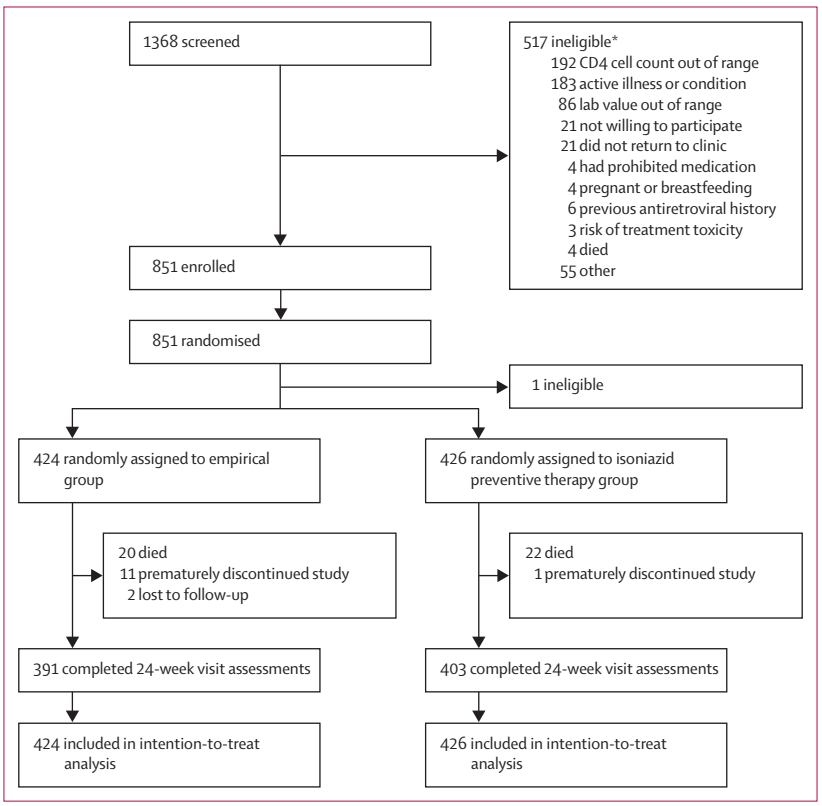


Figure 1: **Trial profile**
*In some cases, more than one reason for ineligibility was provided.

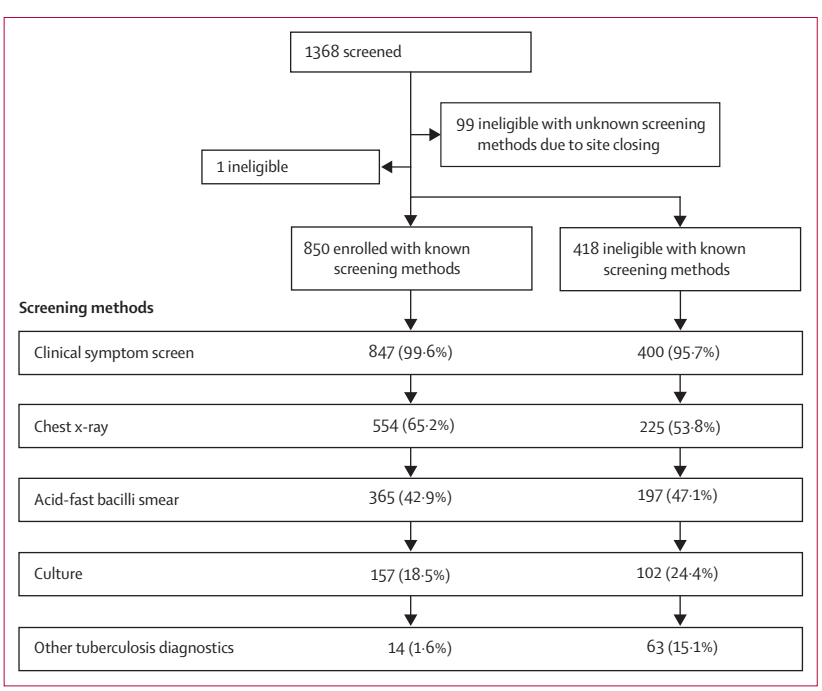


Figure 2: **Screening methods for enrolled and ineligible participants**

For the **AIDS Clinical Trials Group appendix 60** see http://www.hptn.org/web%20documents/HPTN052/Appendix60V1.123Feb2007.pdf

	Empirical therapy (n=424)	Isoniazid preventive therapy (n=426)	All participants (n=850)
Sex			
Male	224 (53%)	226 (53%)	450 (53%)
Female	200 (47%)	200 (47%)	400 (47%)
Race			
Black African or black of African origin	380 (90%)	388 (91%)	768 (90%)
Other	44 (10%)	38 (9%)	82 (10%)
Age (years)	36 (30–42)	35 (30–42)	36 (30–42)
Country			
Malawi	95 (22%)	98 (23%)	193 (23%)
South Africa	86 (20%)	90 (21%)	176 (21%)
Kenya	77 (18%)	75 (18%)	152 (18%)
Haiti	53 (13%)	56 (13%)	109 (13%)
Zimbabwe	25 (6%)	27 (6%)	52 (6%)
Uganda	25 (6%)	24 (6%)	49 (6%)
Peru	20 (5%)	19 (4%)	39 (5%)
Zambia	17 (4%)	19 (4%)	36 (4%)
India	17 (4%)	12 (3%)	29 (3%)
Brazil	9 (2%)	6 (1%)	15 (2%)
CD4 cell count (cells per μL)	18 (9–31)	19 (9–33)	18 (9–32)
HIV-1 RNA $\log_{10}$ (copies per mL)	5·4 (5·0–5·7)	5·3 (4·9–5·7)	5·3 (4·9–5·7)
Stratification factors			
CD4 cell count <25 cells per μL	253 (60%)	257 (60%)	510 (60%)
Hospital admission within the past 30 days	19 (4%)	23 (5%)	42 (5%)
Body-mass index <18·5 kg/m²	120 (28%)	128 (30%)	248 (29%)
Anaemia (haemoglobin <8 g/dL)	28 (7%)	16 (4%)	44 (5%)
WHO stages*			
No stage 3 or 4 events	305 (72%)	309 (73%)	614 (72%)
Stage 3	85 (20%)	77 (18%)	162 (19%)
Stage 4	34 (8%)	40 (9%)	74 (9%)
Clinical symptoms			
Cough lasting for 2 or more weeks	66 (16%)	73 (17%)	139 (16%)
Fever ≥38°C	27 (6%)	22 (5%)	49 (6%)
Haemoptysis in the past 2 weeks	0 (0%)	1 (<1%)	1 (<1%)
Night sweats in the past 2 weeks	32 (8%)	43 (10%)	75 (9%)
Unintentional weight loss in the past 30 days	195 (46%)	220 (52%)	415 (49%)
Enlarged axillary or cervical lymph nodes	38 (9%)	43 (10%)	81 (10%)
At least one tuberculosis symptom reported	237 (56%)	265 (62%)	502 (59%)

Data are n (%) or median (IQR). *Number of participants who had at least one event at baseline.

***Table 1*: Baseline characteristics**

telephone. Those who could not be contacted after this process were defined as lost to follow-up.

Outcomes

The primary endpoint was survival (death or unknown vital status) 24 weeks after randomisation. Secondary endpoints included time to death and AIDS progression, confirmed or probable tuberculosis, grade 3 or 4 signs/symptoms, and grade 3 or 4 lab abnormalities. AIDS progression was defined as any new WHO stage 3 or 4 event occurring more than 2 weeks after study entry. Incident tuberculosis was defined as any diagnosis occurring after entry. Safety outcomes included all signs, symptoms, and laboratory abnormalities meeting grade 3 or 4 criteria per the Division of AIDS toxicity table. All causes of death, AIDS progression events, and tuberculosis cases were externally verified.

Statistical analysis

We calculated a target sample size of 836 to detect a 7·5% difference in the primary event probabilities (15% for isoniazid preventive therapy and 7·5% for empirical) between groups based on a two-sided test of binomial probabilities with 90% power, 5% α level, and 5% inflation of the estimated sample size for interim analyses. For the primary endpoint analysis, an intention-to-treat approach was used with all randomly assigned participants regardless of receiving treatment, except for one participant who was enrolled inadvertently because of an incorrect CD4 cell count at screening. The final analysis was done with a significance level of 5%, which does not account for the number of interim analyses because the original sample size was inflated by 5% for the interim analyses. On and off study deaths (where the participant has stopped participation but is known to be dead) and participants with unknown survival status were included as events in the primary endpoint analysis. Kaplan-Meier estimates of the endpoint probabilities across groups were compared by the z-test. Participants who withdrew consent were censored at the time of their last visit.

Similar methods were used to compare the secondary endpoint probabilities of time to death or AIDS progression, and confirmed or probable tuberculosis between groups. Time to any primary and secondary endpoint was compared by the log-rank test. For the secondary analyses, a per-protocol approach was used with all participants who completed the 24-week assessments included. The Cochran-Mantel-Haenszel test was used to compare the primary endpoint probabilities between groups after stratification by randomisation phase (before and after implementation of screening Xpert MTB/RIF testing) and by the prognostic stratification factors described. Additionally, we assessed the effect of excluding any participants with a positive enrolment sputum Xpert MTB/RIF sample as established by retrospective testing. For the safety analysis, all randomly assigned participants were included and the χ^2 test was used to compare the probabilities of safety and tolerability of antiretroviral therapy and tuberculosis treatment. The National Institute of Allergy and Infectious Diseases international data safety monitoring board monitored the study semi-annually. All analyses were done with SAS version 9.4. This trial is registered with ClincalTrials.gov, number NCT01380080.

	Number of participants	Primary endpoint in empirical group	Primary endpoint in isoniazid preventive therapy group	95% CI for estimated difference in endpoint rates (Kaplan-Meier approach)	p value
All participants	850	22 (5%)	22 (5%)	(–3·05 to 2·94)	0·97
All participants excluding six who were Xpert MTB/RIF positive at baseline	844	21 (5%)	21 (5%)	(–3·00 to 2·89)	0·97
Stratification factors*					
Pre-mandated sputum Xpert MTB/RIF	444	13 (6%)	13 (6%)	NA	0·96
Post-mandated sputum Xpert MTB/RIF	398	9 (5%)	9 (4%)	..	..
CD4 <25 cells per μL	504	17 (7%)	17 (7%)	NA	0·92
CD4 ≥25 cells per μL	338	5 (3%)	5 (3%)	..	..
Poor prognostic factor†	284	13 (9%)	8 (6%)	NA	0·94
No poor prognostic factor	558	9 (3%)	14 (5%)	..	..

NA=not applicable. *A total of 842 participants were included because eight participants who withdrew consent at or before week 24 were excluded. †Poor prognostic factor was defined as presence of at least one of the following: reportable hospital admission within the past 30 days, body-mass index of less than 18·5 kg/m², or anaemia (haemoglobin <8 g/dL)

Table 2: **Death or unknown survival status at week 24**

Role of the funding source

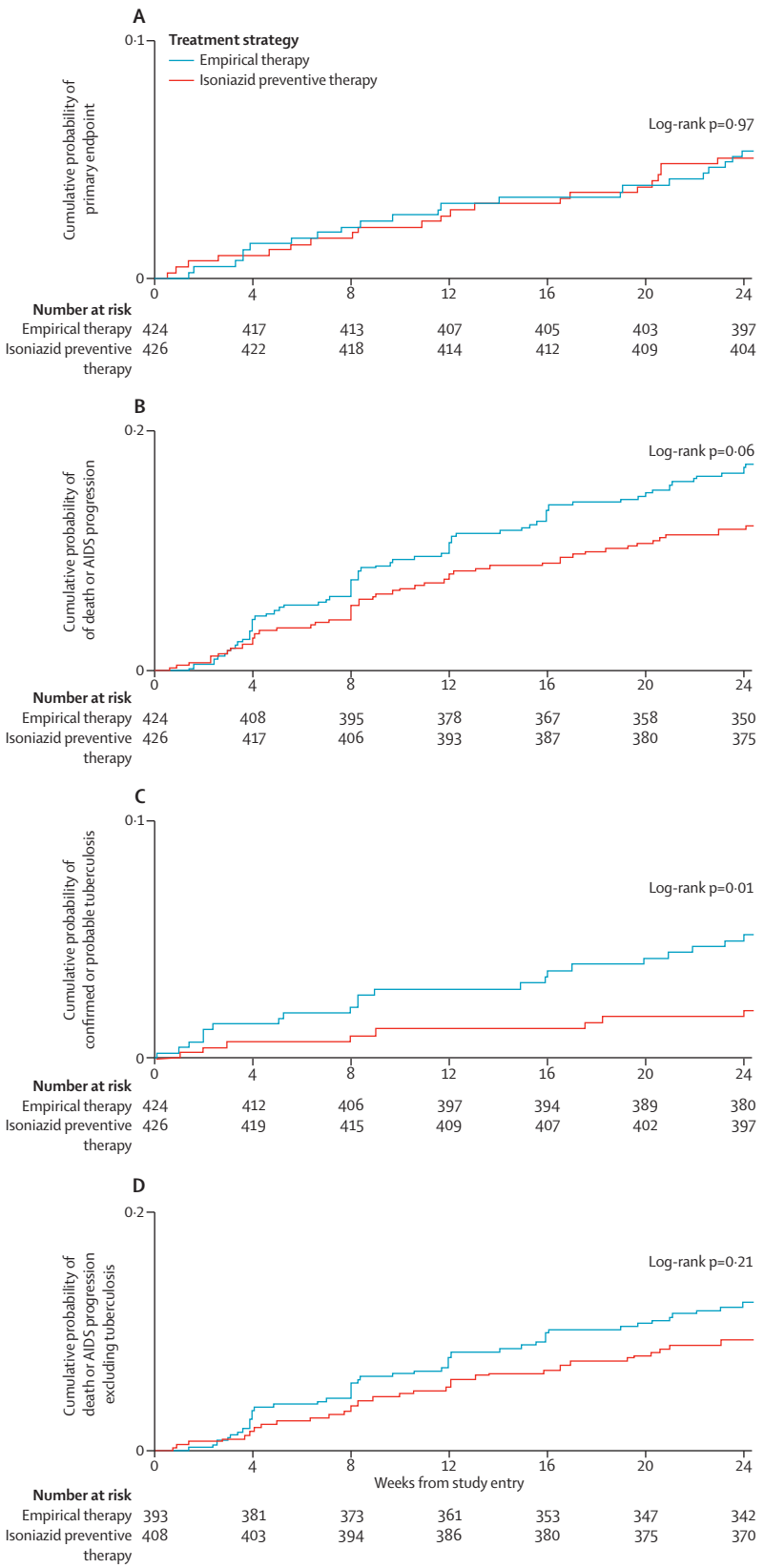
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Oct 31, 2011, and June 9, 2014, 1368 candidates were screened and 851 (62%) were randomly assigned (figure 1). One participant who was randomly assigned to the isoniazid preventive therapy group was later ineligible and was discontinued at day 10 because of a screening CD4 cell count value of 50 cells per μL or more. Hence, 850 participants were enrolled at 18 sites. The most common screening failure reason was having a CD4 cell count value of 50 cells per μL or more, followed by presence of suspected or confirmed tuberculosis cases, and having laboratory values out of range. Patients who were not enrolled were more likely to have an acid-fast bacilli smear, ultrasound, and culture done at screening compared with those who were enrolled (figure 2). Among those screened but ineligible for this study, the number excluded because of tuberculosis suspicion varied across sites from zero in Eldoret (Kenya) and Rio de Janeiro (Brazil) to ten (56%) in Port-au-Prince (Haiti). Overall, ten of 18 sites excluded more than 30% of screening failures because of confirmed or probable tuberculosis. Among 1268 participants screened for the study, 1247 (98%) had protocol-mandated symptom screening, chest radiography was done in 779 (61%), sputum acid-fast bacilli smear in 562 (44%), culture in 259 (20%), and other diagnostics in 77 (6%). Of those screened, 26 patients were excluded because of a positive Xpert MTB/RIF assay. Among those enrolled, about 85% could produce sputum at baseline.

Baseline characteristics of 850 enrolled participants (424 in empirical group and 426 in isoniazid preventive therapy group) were similar across groups (table 1). Participants had highly advanced HIV disease with a median (IQR) CD4 cell count of 18 cells per μL (9–32). Of 448 (53%) who were enrolled before sputum Xpert MTB/RIF assay screening, 379 (45%) had retrospective testing with Xpert MTB/RIF and six (2%) were positive, three in each group. Among the 850 enrolled participants, 502 (59%) had at least one positive result on symptom screen before enrolment in the trial, with unintentional weight loss being the most commonly reported symptom, followed by cough for more than 2 weeks (table 1).

At week 24, both groups had 22 primary events, resulting in the same primary endpoint rate of 5·2% (95% CI 3·5–7·8 for the empirical group and 3·4–7·8 for the isoniazid preventive therapy group; p =0·97) and resulting in an absolute risk difference of –0·06% (95% CI –3·05% to 2·94%). All primary endpoints were deaths except for two unknown vital status events in the empirical group. The death rates between the study groups did not differ significantly after treating the two participants as censored cases in sensitivity analysis (20 [4·8%] in the empirical group *vs* 22 [5·2%] in the isoniazid preventive therapy group; p=0·78). Among the ten countries with at least one site, eight reported at least one death and the primary endpoint rates by group were generally similar across countries. Although mortality was higher in those with a CD4 cell count of less than 25 cells per μL and those with poor prognostic factors, the event rates were similar across groups for the stratification factors before and after implementation of sputum Xpert MTB/RIF testing, or after excluding participants with retrospectively identified positive sputum Xpert MTB/RIF tests (table 2). The time to the primary event did not differ between groups (figure 3).



Causes of death included HIV-associated infections (17 in empirical group, 11 in isoniazid preventive group), non-HIV diagnoses (five in isoniazid preventive group), renal toxicity attributed to tenofovir (one in isoniazid preventive group), unknown in six cases (two in empirical group, four in isoniazid preventive group), and motor vehicle accident (one in isoniazid preventive group; appendix). The most common HIV-associated causes of death were cryptococcal meningitis (n=4), Kaposi's sarcoma (n=3), and extrapulmonary tuberculosis (n=3).

By week 24, the empirical group had a higher rate of death or AIDS progression than the isoniazid preventive therapy group (72 [17%] *vs* 53 [13%]; p=0·06) and the time to death or AIDS progression was more rapid in the empirical group (figure 3). This result was mainly due to an increased incidence of tuberculosis (31 participants in the empirical group and 18 participants in the isoniazid preventive therapy group; p=0·01), including both pulmonary and extrapulmonary disease (appendix). The time to confirmed or probable tuberculosis in the empirical group was also more rapid (figure 3). The time to death or AIDS progression, if confirmed or probable tuberculosis was excluded, did not differ between groups (figure 3). Self-reported adherence to study medications was similar across groups at all weeks apart from in the empirical group at 8 weeks, which reported lower than 100% adherence to tuberculosis drugs (360 [88%] in the empirical group *vs* 383 [93%] in the isoniazid preventive therapy group; p=0·03). The empirical group also had more premature discontinuations of tuberculosis drugs by week 24 (47 discontinued in the empirical group *vs* 18 in the isoniazid preventive therapy group). A viral load of less than 400 copies per mL was achieved by 309 (84%) of 370 participants in the empirical group and 322 (85%) of 378 participants in the isoniazid preventive therapy group. The median CD4 change at 24 weeks was 96 (IQR 55–147) in the empirical group and 102 (60–159) in the isoniazid preventive therapy group (p=0·25 by Wilcoxon test).

Safety measures were also similar across groups. Grade 3 or 4 signs or symptoms occurred in 50 (12%) participants in the empirical group and 46 (11%) in the isoniazid preventive therapy group. Grade 3 or 4 laboratory abnormalities occurred in both groups (table 3). Haematological abnormalities were most common, followed by hepatic abnormalities (table 3). Of the 49 incident cases of tuberculosis, there was no evidence of differential increased drug resistance by study group. Drug resistance to at least one tuberculosis drug occurred in six participants, three in each group. In the empirical group, the resistance profiles of the three participants were isoniazid/ethambutol, isoniazid/rifampin/

***Figure 3*: Kaplan-Meier plots for time to primary and secondary endpoint**
(A) Time to primary endpoint (death or unknown status) by treatment strategy. (B) Time to death or AIDS progression by treatment strategy. (C) Time to confirmed or probable tuberculosis by treatment strategy. (D) Time to death or AIDS progression (excluding confirmed and probable tuberculosis) by treatment strategy.

	Empirical therapy (n=424)			Isoniazid preventive therapy (n=427)			All participants (n=851)		
	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades
Any chemical abnormalities	21 (5 %)	5 (1 %)	26 (6%)	20 (5 %)	9 (2%)	29 (7 %)	41 (5 %)	14 (2 %)	55 (6 %)
Any gaseous chemical abnormalities	1 (<1%)	0	1 (<1%)	0	0	0	1 (<1%)	0	1 (<1%)
Hydrogen ion concentration	1 (<1%)	0	1 (<1%)	0	0	0	1 (<1%)	0	1 (<1%)
Any general chemical abnormalities	20 (5%)	5 (1%)	25 (6%)	20 (5%)	9 (2%)	29 (7%)	40 (5%)	14 (2%)	54 (6%)
Albumin	11 (3%)	0	11 (3%)	6 (1%)	0	6 (1%)	17 (2%)	0	17 (2%)
Alkaline phosphatase	1 (<1%)	0	1 (<1%)	10 (2%)	1 (<1%)	11 (3%)	11 (1%)	1 (<1%)	12 (1%)
Bicarbonate	2 (<1%)	0	2 (<1%)	0	0	0	2 (<1%)	0	2 (<1%)
Calcium	1 (<1%)	0	1 (<1%)	2 (<1%)	0	2 (<1%)	3 (<1%)	0	3 (<1%)
Carbon dioxide	0	0	0	0	1 (<1%)	1 (<1%)	0	1 (<1%)	1 (<1%)
Sodium	10 (2%)	5 (1%)	15 (4%)	9 (2%)	7 (2%)	16 (4%)	19 (2%)	12 (1%)	31 (4%)
Any endocrine events	1 (<1%)	0	1 (<1%)	0	0	0	1 (<1%)	0	1 (<1%)
Any general endocrine events	1 (<1%)	0	1 (<1%)	0	0	0	1 (<1%)	0	1 (<1%)
Uric acid	1 (<1%)	0	1 (<1%)	0	0	0	1 (<1%)	0	1 (<1%)
Any haematological events	38 (9 %)	27 (6 %)	65 (15 %)	46 (11 %)	13 (3 %)	59 (14 %)	84 (10 %)	40 (5 %)	124 (15 %)
Any haematological coagulation	0	2 (<1%)	2 (<1%)	3 (1%)	1 (<1%)	4 (1%)	3 (<1%)	3 (<1%)	6 (1%)
Low platelet count	0	2 (<1%)	2 (<1%)	3 (1%)	1 (<1%)	4 (1%)	3 (<1%)	3 (<1%)	6 (1%)
Any haematological red blood cell event	12 (3%)	9 (2%)	21 (5%)	20 (5%)	4 (1%)	24 (6%)	32 (4%)	13 (2%)	45 (5%)
Low haemoglobin concentration	12 (3%)	9 (2%)	21 (5%)	20 (5%)	4 (1%)	24 (6%)	32 (4%)	13 (2%)	45 (5%)
Any haematological white blood cell or differential event	31 (7%)	18 (4%)	49 (12%)	28 (7%)	9 (2%)	37 (9%)	59 (7%)	27 (3%)	86 (10%)
Low absolute neutrophil count	33 (8%)	16 (4%)	49 (12%)	26 (6%)	9 (2%)	35 (8%)	59 (7%)	25 (3%)	84 (10%)
Low white blood cell count	6 (1%)	2 (<1%)	8 (2%)	4 (1%)	1 (<1%)	5 (1%)	10 (1%)	3 (<1%)	13 (2%)
Any liver or hepatic event	17 (4 %)	9 (2 %)	26 (6 %)	18 (4 %)	11 (3 %)	29 (7 %)	35 (4 %)	20 (2 %)	55 (6 %)
Serum glutamic-oxaloacetic transaminase	16 (4%)	4 (1%)	20 (5%)	16 (4%)	8 (2%)	24 (6%)	32 (4%)	12 (1%)	44 (5%)
Serum glutamic-pyruvic transaminase	7 (2%)	6 (1%)	13 (3%)	14 (3%)	6 (1%)	20 (5%)	21 (2%)	12 (1%)	33 (4%)
Total bilirubin	4 (1%)	2 (<1%).	6 (1%)	0	3 (1%)	3 (1%)	4 (<1%)	5 (1%)	9 (1%)
Any renal event	2 (<1%)	1 (<1%)	3 (1 %)	3 (1 %)	2 (<1%)	5 (1 %)	5 (1 %)	3 (<1%)	8 (1 %)
Creatinine	2 (<1%)	1 (<1%)	3 (1%)	3 (1%)	2 (<1%)	5 (1%)	5 (1%)	3 (<1%)	8 (1%)
Any event	59 (14 %)	40 (9 %)	99 (23 %)	66 (15 %)	31 (7 %)	97 (23 %)	125 (15 %)	71 (8 %)	196 (23 %)

Multiple events could be reported in a participant.

Table 3: **Grade 3 or higher laboratory events by week 24**

ethambutol, and streptomycin/rifampin/isoniazid/ethambutol whereas in the isoniazid preventive therapy group, the resistance profiles of the three participants were isoniazid only, streptomycin/rifampin/isoniazid/ethambutol, and streptomycin/rifampin/isoniazid/ethambutol/pyrazinamide. The participants switched to appropriate tuberculosis treatment according to local guidelines after the resistance was identified.

Despite potential benefits of rifampin for severe bacterial infections, the incidence of such infections did not differ significantly by group (37 [9%] in the empirical group and 52 [12%] in the isoniazid preventive therapy group, p=0·095; appendix). Tuberculosis-immune reconstitution inflammatory syndrome was adjudicated with AIDS Clinical Trial Group definitions by the external endpoint panel. 19 (2%) tuberculosis-immune reconstitution inflammatory syndrome cases were reported (nine in the empirical group and ten in the isoniazid preventive therapy group). Of these 19 cases, 13 had confirmed antiretroviral therapy unmasking tuberculosis-immune reconstitution inflammatory syndrome (ie, tuberculosis was not identified before tuberculosis-immune reconstitution inflammatory syndrome diagnosis; six in the empirical group and seven in the isoniazid preventive therapy group), and five had probable antiretroviral therapy unmasking tuberculosis-immune reconstitution inflammatory syndrome (two in the empirical group and three in the isoniazid preventive therapy group), and one participant in the empirical group had probable paradoxical tuberculosis-associated tuberculosis-immune reconstitution inflammatory syndrome (tuberculosis diagnosis was known before the tuberculosis-associated tuberculosis-immune reconstitution inflammatory syndrome diagnosis and manifested as worsening of tuberculosis signs or symptoms).

See Online for appendix

Discussion

In this large, multisite, randomised clinical trial, empirical tuberculosis therapy did not reduce early mortality compared with administration of isoniazid preventive therapy in individuals with highly advanced HIV disease initiating antiretroviral therapy in outpatient settings where tuberculosis incidence is high. Furthermore, despite enrolling participants with very low CD4 cell counts, we observed a mortality rate that was substantially lower than that observed in previous studies from similar settings.[2] We also observed an increased risk of AIDS progression and specifically tuberculosis in the empirical group. Taken together, the results support the use of standardised tuberculosis screening procedures in patients with advanced HIV disease presenting for antiretroviral therapy initiation and indicate that, in those without a diagnosis of tuberculosis after screening, there is no added benefit of empirical tuberculosis therapy compared with provision of isoniazid preventive therapy alone. This study effectively shows that the combination of isoniazid preventive therapy with antiretroviral therapy is safe when used to prevent tuberculosis and early mortality in very advanced HIV disease.

We hypothesised that empirical tuberculosis therapy would more effectively treat those with subclinical active tuberculosis and thereby reduce early mortality. Numerous studies done pre-mortem and post mortem have identified tuberculosis as the major cause of mortality in those with advanced HIV disease who are initiating antiretroviral therapy in sub-Saharan Africa, India, Haiti, and parts of South America.[2,6] An additional hypothesised effect of empirical tuberculosis therapy relates to a potentially more durable tuberculosis preventive effect of isoniazid and rifampin compared with isoniazid alone.[16] Lastly, by virtue of the use of rifampin, empirical tuberculosis treatment could also plausibly provide benefit in terms of prevention or early treatment of severe bacterial infections. However, we found a definitive lack of benefit of empirical therapy on mortality outcomes. This finding probably resulted partly from the exclusion of many tuberculosis cases by the study's systematic tuberculosis screening approach, as a third of screened participants were excluded for suspected active tuberculosis. Furthermore, although the median CD4 cell count of the study population was very low, systematic non-referral of sicker patients or those with very high tuberculosis suspicion to the study might have resulted in exclusion of candidates with poor prognosis. Our study still encountered substantial incident tuberculosis, but we also observed that fewer participants diagnosed with tuberculosis after antiretroviral therapy initiation died during the 24 weeks of follow-up across both groups. This finding contrasts sharply with the strong association previously observed between prevalent and incident tuberculosis after antiretroviral therapy initiation and early mortality in HIV-infected outpatients initiating antiretroviral therapy.[3,17] This lower mortality is notable, given the highly advanced HIV disease of the cohort, but provides solid evidence to suggest that empirical tuberculosis therapy does not provide a mortality benefit over isoniazid preventive therapy even in outpatients with profound immunosuppression who remain without a tuberculosis diagnosis after screening.

Other observational studies and clinical trials have documented early mortality rates of 15% or higher,[2,18,19] which is substantially greater than the 5% documented in this study. In addition to possible effects of screening and referral patterns, this low mortality rate might also relate to the fact that all participants received isoniazid, a rapidly bactericidal agent,[20] which can reduce the risk of tuberculosis in HIV-positive patients.[21–23] Although isoniazids effect on survival is uncertain in patients with severe HIV immunosuppression, two observational studies from South Africa and a cluster-randomised trial in Brazil found that isoniazid preventive therapy reduced early mortality and incidence of a combined endpoint of tuberculosis and mortality in HIV-positive individuals.[24–26] The TEMPRANO study,[15] a randomised, 2×2 factorial designed clinical trial assessing antiretroviral therapy and isoniazid preventive therapy in adults with median baseline CD4 cell count of approximately 460 cells per μL, found that isoniazid preventive therapy resulted in a 35% reduction in severe HIV morbidity. To date, no other trial including isoniazid preventive therapy and antiretroviral therapy initiation in HIV-positive individuals has examined a similarly large population of individuals with highly advanced HIV disease. This distinguishing characteristic of the REMEMBER trial is important because although isoniazid is recommended by WHO for HIV-positive adults, its uptake and implementation has been very low due partly to concerns about excluding active tuberculosis in advanced HIV disease, and associated fears of generating drug resistance. Deferring isoniazid preventive therapy for some months in patients with advanced HIV has been proposed as a strategy to address any potential resistance risk associated with early incident tuberculosis.[27] However, although the number of incident tuberculosis cases in this study limits formal analyses of isoniazid resistance, the prescribed 6-month course of isoniazid preventive therapy was well tolerated and discontinuations were rare when initiated near the time of antiretroviral therapy initiation. Thus, although our study did not include a placebo group, these results indicate that isoniazid preventive therapy plus antiretroviral therapy can be safely implemented in patients with highly advanced HIV disease who are not diagnosed with

tuberculosis after screening. This is consistent with the WHO's latest guidance to provide isoniazid preventive therapy regardless of CD4 cell count for all HIV-infected adults and adolescents.[14] Repeated symptom screening for tuberculosis at follow-up visits after isoniazid preventive therapy initiation, also recommended by WHO,[14] should be implemented to detect incident tuberculosis as early as possible on antiretroviral therapy.

The increased risk of AIDS progression and specifically tuberculosis seen in the empirical group was unexpected. Provision of four-drug tuberculosis therapy to patients without a known tuberculosis diagnosis plausibly could lead to adverse events and reduced adherence to antitubercular therapy or antiretroviral therapy, either of which could result in an increased risk of AIDS progression. Although self-reported adherence to tuberculosis therapy and antiretroviral therapy, and virological and immunological responses to antiretroviral therapy, were similar across groups for all visits except week 8, premature tuberculosis drug discontinuation rates were more common in the empirical group. A previous study has suggested that the combination of isoniazid/rifampin might have more potent and durable protection against the development of tuberculosis and death than isoniazid alone, but multidrug regimens for treatment of latent tuberculosis infection are also associated with increased risk of discontinuation.[21] Another potential explanation for the increased rate of tuberculosis in the empirical group is diagnostic suspicion bias, where knowledge of tuberculosis treatment status led to more aggressive use of tuberculosis diagnostics or more liberal tuberculosis diagnosis in participants randomised to the empirical group. Unmasking tuberculosis-immune reconstitution inflammatory syndrome was also uncommon in both groups and does not appear to explain this difference in incident tuberculosis. Nonetheless, given the lack of clinical benefit of the empirical therapy, the finding of potential harm should be carefully considered by providers when assessing similar patient populations.

Notably our study population of adults with advanced HIV disease (CD4 cell count of less than 50 cells per μL) continues to be encountered in HIV programmes globally, despite evolving guidance to start antiretroviral therapy at higher CD4 cell counts.[14] The median CD4 cell count for initiating antiretroviral therapy in programmes in low-income and middle-income settings remains below 200 cells per μL.[3,28] This population with a low CD4 cell count is the group at highest risk of developing and dying from tuberculosis. By focusing on individuals with advanced HIV disease, our study provides valuable evidence that systematic screening for tuberculosis with standard measures that might or might not include GeneXpert might enable safe and effective initiation of isoniazid preventive therapy and antiretroviral therapy together in settings with a high burden of HIV and tuberculosis.

Our study has some limitations. Study treatment was not blinded to providers or participants, such that knowledge of study group could both influence patient acceptance of a multidrug combination treatment or providers' diagnostic suspicion for tuberculosis. However, the unblinded approach enabled a pragmatic assessment of how this treatment strategy might work in non-trial settings, where participants without tuberculosis after screening would be asked to initiate four-drug tuberculosis therapy. The conduct of the study in multiple sites where early mortality rates are high and tuberculosis is endemic is a major strength, but the results might not be generalisable to settings where systematic tuberculosis screening is not done, or where limited resources prevent close follow-up and early tuberculosis diagnosis after antiretroviral therapy initiation. Additionally, the results from this study in outpatients initiating antiretroviral therapy might be not be generalisable to sicker inpatient populations with higher mortality rates, where the prevalence of tuberculosis at autopsy has approached 50%.[6] However, randomised trials of empirical tuberculosis therapy in settings with inpatients with highly advanced HIV would address a different research question, and might have different concerns regarding equipoise. Another limitation was that we did not collect data for all eligible patients who could have potentially enrolled but who were not referred to the trial, limiting our ability to place this strategy in a broader context of HIV patient care. Nonetheless, similarly low mortality rates might be achievable in routine care settings, given that the study's screening methods and follow-up schedule were based largely on WHO and local treatment guidelines.[14] Although many settings might not have universal access to the Xpert MTB/RIF assay, mortality rates in this study were similar before and after mandatory sputum Xpert MTB/RIF testing at screening was implemented, and after excluding tuberculosis cases identified retrospectively with the Xpert MTB/RIF assay. This result is consistent with data indicating that the use of the Xpert MTB/RIF assay might not reduce mortality in patients with HIV.[11–13] Furthermore, the rationale for empirical tuberculosis therapy is primarily based on high rates of undiagnosed tuberculosis in patients presenting for care, which partly depends on the availability of accurate tuberculosis diagnostics and assessments done before antiretroviral therapy initiation, along the entire cascade of HIV care. Novel tuberculosis diagnostics, such as the urinary lipoarabinomannan assay, which has approximately 67% sensitivity in patients with CD4 cell counts of less than 50 cells per μL,[29] has recently been shown to reduce mortality and the use of empirical tuberculosis treatment in patients admitted to hospital when used as

an additional diagnostic test[30] and might decrease the rationale for empirical tuberculosis therapy.

In summary, our study found that empirical tuberculosis treatment did not reduce early mortality in outpatients with advanced HIV disease compared with provision of isoniazid preventive therapy. In patients with advanced HIV disease in settings where tuberculosis incidence is high, systematic tuberculosis screening before antiretroviral therapy initiation and implementation of isoniazid preventive therapy near the time of antiretroviral therapy initiation should be urgently pursued.

Contributors

MCH, GPB, AG, JK, and AZ did the literature search. MCH, GPB, JB, EH, AZ, JK, and AG designed the study. MCH, AM, CR, FKK, SB-F, DL, MN, KN, JH, PM, GH, PDL, JRL, LM, JA, VM, VGV, SP, NK, and JK were responsible for participant recruitment. MCH, GPB, AM, CR, FKK, SB-F, DL, MN, KN, JH, PM, GH, PDL, JRL, LM, JA, VM, VGV, SP, and NK collected the data. MCH, GPB, SM, XS, AM, CR, FKK, SB-F, DL, MN, KN, JH, PM, GH, PDL, JRL, LM, JA, VM, VGV, SP, NK, JB, LJ, EH, AZ, JK, and AG interpreted the data. MCH, GPB, SM, XS, AZ, and AG drafted the manuscript. MCH, GPB, SM, XS, AM, CR, FKK, SB-F, DL, MN, KN, JH, PM, GH, PDL, JRL, LM, JA, VM, VGV, SP, NK, JB, LJ, EH, AZ, JK, AG revised the manuscript and contributed intellectually. SM and XS analysed the data and generated the figures. LJ managed the data.

Declaration of interests

We declare no competing interests.

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